



General

Guideline Title

Intravesical instillation with mitomycin C or bacillus Calmette-Guérin in non-muscle invasive bladder cancer.

Bibliographic Source(s)

Vahr S, De Blok W, Love-Rettinger N, Thoft Jensen B, Turner B, Villa G, Hrbáček J. Intravesical instillation with mitomycin C or bacillus Calmette-Guérin in non-muscle invasive bladder cancer. Arnhem (The Netherlands): European Association of Urology Nurses (EAUN); 2015 Mar. 88 p. [178 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Level of evidence (LE) (1a-4) and grade of recommendation (GR) (A-C) are defined at the end of the "Major Recommendations" field.

Safety

Patient Safety

Employers must assess the risk of handling antineoplastic and biological drugs and take suitable precautions to protect employees by identifying the hazards, and deciding who might be harmed and how. (LE=4, GR=C)

Health care workers involved in the preparation and administration of intravesical instillation medication should always follow local and hospital safety procedures to prevent exposure of patients and personnel to hazardous medication. (LE=4, GR=C)

Instillation medication should be prepared in a pharmacy or biological safety cabinet (BSC) to prevent exposure. (LE=4, GR=C)

To reduce risk of exposure during drug administration, a closed system is recommended. (Clark & Sessink, 2013) (LE=3, GR=B)

To reduce risk of exposure during drug preparation and administration personal protective clothing

should be worn in accordance with local and hospital safety procedures. (Brixey, 1988; Occupational Safety and Health Administration [OSHA], 1999; McDiarmid et al., 2010; Meijster et al., 2006; Yoshida et al., 2009; Boiano & Hull, 2001; Lawson et al., 2012; Fransman, 2006; Landeck, Gonzalez, & Koch, 2014; Boiano, Steege, & Sweeney, 2014) (LE=3, GR=B)

All material that has been exposed to medication used in intravesical instillation should be considered as contaminated and disposed of in accordance with local and hospital regulations, in a container specifically used for chemotherapeutic waste. (LE=4, GR=C)

Reusable materials and furniture at risk of being contaminated during the intravesical instillation should be protected by protective absorbent pads. (LE=4, GR=C)

All personnel handling, transporting and cleaning materials used for intravesical instillations must be properly trained on the content and the risks involved. (LE=4, GR=C)

Nurses should educate patients and care givers how to deal with the risk of exposure during and after the intravesical instillation. (LE=4, GR=C)

Nurses should advise patients not to become pregnant within 6 months after the treatment with bacillus Calmette-Guérin (BCG) or mitomycin C (MMC). (LE=4, GR=C)

Pregnant or lactating health care workers taking care of patients being treated with antineoplastic agents (MMC) should follow local guidelines when preparing or administering the drugs, clean spillage or waste and prevent contact with the patient's urine, stools, vomit or heavy perspiration. (LE=4, GR=C)

Nurse Education Prior to Instillation

Nurses should maintain a universal standard of education, understanding and competence in relation to intravesical therapies. (LE=4, GR=C)

All staff involved in handling hazardous drugs must receive training on the hazards. (LE=4, GR=C)

Nurse specialist administering intravesical therapies needs to be trained and assessed by a competent practitioner. (LE=4, GR=C)

In countries where nurses have a license to prescribe medication the decision to initiate intravesical therapies should be made by the multi-disciplinary team. (LE=4, GR=C)

Training records should be maintained. (LE=4, GR=C)

Principles of Management of Nursing Interventions

Preparation of Bladder Instillation Medication

BCG should not be prepared in areas where intravenous drugs are prepared. (Stone et al., 1995) (LE=3, GR=B)

Administration of Intravesical Instillation

In intravesical instillations an intermittent catheter with the smallest size possible should be used. (Geng et al., 2012) (LE=4, GR=C)

In intravesical instillations a luer lock catheter is recommended to reduce risk of exposure. (LE=4, GR=C)

If possible choose a hydrophilic catheter to reduce risk of discomfort, trauma and infection. (Cindolo et al., 2004; Hedlund et al., 2001; De Ridder et al., 2005) (LE=3, GR=B)

Use 10-15 ml of lubricants when a non-hydrophilic catheter is used. (Geng et al., 2012; Loertzer et al., 2001) (LE=2a, GR=B)

Patient Education

Before any intravesical therapy begins, nurses need to inform patients and care givers about the therapy, fluid intake, safety precautions that should be taken and any side effects that may occur. (LE=4, GR=C)

The educator should assess the best method of learning for each individual patient. (LE=4, GR=C)

Complications and Side Effects

Catheter-Associated Bacteriuria

Aseptic technique should be used when inserting the catheter before intravesical instillation. (Tenke et al., 2008; Biering-Sørensen, Bagi, & Høiby, 2001; Wyndaele, 2002) (LE=3, GR=B)

Health care professionals should be constantly aware of their hand hygiene and observe protocols on hand hygiene. (Tenke et al., 2008; Biering-Sørensen, Bagi, & Høiby, 2001) (LE=1b, GR=A)

Side Effects of MMC

To ensure that the bladder is empty before instilling BCG or MMC and ensure meticulous homeostasis at the end of bladder tumour resection. (Griffin & Holzbeierlein, 2013) (LE=3, GR=C)

Side Effects of Mitomycin C (MMC) (Griffin & Holzbeierlein, 2013; De Groot & Conemans, 1991; Mertens et al., 2012)			
MMC – Local	Nursing Solution	LE	GR
Chemical cystitis	Treat these side effects symptomatically. Agents such as phenazopyridine and anticholinergics can be used in more bothersome cases. Powdered opium and belladonna alkaloids in a suppository form can also be used during instillation to provide relief of spasms and discomfort, and to help with retention of the intravesical agent.	3	C
MMC – Systemic	Nursing Solution	LE	GR
Skin toxicity	Remove exposing agent Use antihistamines and corticosteroids	3	C
Myelosuppression	Blood products may be given in severe cases	3	C
Intraperitoneal extravasation	Call the doctor for immediate evacuation of the agent followed by cystography	3	C
Extraperitoneal extravasation	Fluid collections should be drained with a catheter Initiate antibiotic prophylaxis	3	C

Common Side Effects of BCG

Dose reduction to 1/3 of the usual dose for the reduction of side effects is no longer recommended. (Oddens et al., 2013; Brausi et al., 2014) (LE=1b, GR=A)

Patient Quality of Life (QoL)

Impact of Intravesical Instillations on the Patient Reported Outcome

When assessing patients before treatment predictors for intermittent loss of health-related quality of life (HRQoL) such as autonomy in daily life, comorbidities, older age and family situation should be assessed. (Matsuda et al., 2004) (LE=3, GR=B)

The multi-professional team should inform, educate, comfort and motivate non-muscle invasive bladder cancer (NMIBC) and carcinoma *in situ* (CIS) patients regarding treatment impact on global health and when to expect to regain initial HRQoL status. (Yoshimura et al., 2005; Wei et al., 2014) (LE=3, GR=B)

Patients should be informed pre-procedure that:

Most patients will regain initial HRQoL status within one year. (Yoshimura et al., 2005) (LE=3, GR=B)

Most domains included in global HRQoL will return to initial levels except from physical function within one year. (Gontero et al., 2013) (LE=2b, GR=B)

Social function, role and emotional functions, which are also associated with working status, are most severely impaired at the first cycle of BCG. (Yoshimura et al., 2005) (LE=3, GR=B)

Definitions

Level of Evidence (LE)

Level	Type of Evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Grade of Recommendation (GR)

Grade	Type of Evidence - Nature of Recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Non-muscle invasive bladder cancer (NMIBC)

Guideline Category

Counseling

Management

Prevention

Treatment

Clinical Specialty

Nursing

Oncology

Urology

Intended Users

Advanced Practice Nurses
Nurses

Guideline Objective(s)

- To improve current standards of urological nursing care by directly helping members of the European Association of Urology Nurses (EAUN) develop or update their expertise
- To provide guidelines with recommendations that clearly state the level of evidence of each procedure, with the aim of improving current practices and delivering a standard and reliable protocol
- To help nurses identify potential problem areas and efficiently carry out effective patient care
- To highlight the psychological and social aspects unique to the experience of patients undergoing intravesical instillations as aspects that have influence on quality of life (QoL)
- To support nurses and practitioners who are already assessed as competent in the procedure of intravesical instillation
- To prevent unintended harm to patients or caregivers, and to enhance treatment compliance by addressing patient-related outcomes
- To provide guidance for the standard intravesical instillation of mitomycin C (MMC) and bacillus Calmette-Guérin (BCG), for health care professionals, patients and their families
- To describe evidence-based or best practice for safe administration and handling of the agents, based on articles found in a literature search, USA and European Union (EU) regulations, and consensus in the Working Group

Target Population

Adults with non-muscle invasive bladder cancer (NMIBC) treated with intravesical instillation

Interventions and Practices Considered

1. Implementation of precautions to protect employees and patients from exposure to antineoplastic and biological drugs
2. Nurse education and ensuring nursing competency in intravesical instillation
3. Avoiding preparation of bacillus Calmette-Guérin (BCG) in areas where intravenous drugs are prepared
4. Catheter use for intravesical administration, including use of aseptic technique
5. Patient and care giver education on risks and cautions of intravesical therapy
6. Management of side effects and complications of BCG and mitomycin C (MMC)
7. Assessment of patient quality of life (QoL) and offering reassurance

Major Outcomes Considered

- Complications of intravesical instillation (including bacteriuria)
- Side effects/toxicity of medications used for intravesical administration
- Patient quality of life (QoL)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search

The information offered in these guidelines was obtained through a systematic literature search and a review of current procedures undertaken in various member countries of the European Association of Urology Nurses (EAUN).

A search of the medical literature was conducted using Medline (Ovid SP), (1946 to 21 November 2014), EMBASE (OVID SP) (1974 to 21 November 2014), CINAHL (1982 to 21 November 2014), Cochrane Central Register of Controlled Trials and the Cochrane Health Technology Assessment databases (from inception to November 2014).

Both medical subject headings (MeSH) and free-text terms, as well as variations of root words, were searched. Key terms related to "non-muscle invasive bladder cancer" were combined using the set operator AND key terms related to "bladder instillation" AND key terms related to "mitomycin or bacillus Calmette-Guérin (BCG)". MeSH terms included non-muscle invasive bladder cancer, bladder tumor, bladder neoplasms, bladder cancer, bladder carcinoma, transitional cell carcinoma, carcinoma in situ; mitomycins, mitomycin, mitomycin C, BCG vaccine; bladder irrigation, therapeutic irrigation, intravesical drug administration, and administration, intravesical.

Non-English-language studies, animal or *in vitro* studies, conference proceedings, and paediatric studies were excluded.

The search was based on problem, intervention, comparison, outcome (PICO) questions formulated by the Working Group (see Appendix 14.11 in the original guideline document).

Limitation of the Search

Limitations

English language

Adults

The search results were not limited to randomised controlled trials (RCTs), controlled clinical trials, meta-analyses or systematic reviews. In all databases, output was limited to human studies, adults aged ≥ 19 years, 1946 to July 2013, and English-language publications.

Additional searches were not limited to any level of evidence (LE), and European Union (EU), USA and national regulations were also used.

Exclusion Criteria During Search

Painful bladder syndrome

Exclusion Criteria When Selecting the Abstracts

Treatment planning

Tumour recurrence

In vitro studies

Studies comparing effects of treatment with mitomycin C (MMC)/BCG with those of other chemotherapy neoadjuvant medication, thermo chemotherapy, and electromotive drug approach.

Search Results

The initial search was done in August 2013 at McMaster University, Hamilton, Ontario, Canada, and repeated in November 2014. See Flowchart 1 in the original guideline document for search results.

It was a policy decision to restrict the search in the way described, although the Group was aware that more complex strategies were possible, and would be encouraged in the context of a formal systematic review. In the process of working with the articles, new references were found and added to the reference list, if they were relevant to the topic and cited in the text.

Number of Source Documents

References included: 178 (see the Flowchart 1 in the original guideline document for a breakdown of the number of articles identified and excluded during each stage of the search process)

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence (LE)

Level	Type of Evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Rating System

The recommendations provided in this document are based on a rating system modified from that produced by the Oxford Centre for Evidence-based Medicine (OCBM) in 2011. External data extractors recruited from the European Association of Urology (EAU) used the EAU data-extraction system for critical assessment of the papers identified.

Whenever possible, the Working Group graded treatment recommendations using a three-grade system (grade of recommendation; GR A-C) and inserted levels of evidence to help readers assess the validity of the statements made. The aim of this practice is to ensure a clear transparency between the underlying evidence and the recommendations given. This system is further described in the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields.

Some of the literature was not easy to grade. However, if the Working Group thought that the information would be useful in practice, it was ranked as level of evidence (LE) 4 and GR C. Low-level evidence indicated that no higher level evidence was found in the literature when writing the guidelines, but cannot be regarded as an indication of the importance of the topic or recommendation for daily practice.

The literature used in these guidelines included qualitative research, but because there is no systematic ranking for these types of studies, the qualitative studies were all graded LE 4.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The European Association of Urology Nurses (EAUN) Guidelines Working Group for intravesical instillation have prepared these guidelines to help nurses assess evidence-based management and incorporate the recommendations into their clinical practice. The Working Group consists of a multidisciplinary team of nurse specialists as well as a urologist.

The scope of these guidelines was established at the start of the guidelines process. Fifteen patient, intervention, comparison and outcome (PICO) questions (see Addendum 14.11 in the original guideline document for a description) were posed to guide the literature review process.

The recommendations in these guidelines are based on synthesis of evidence from the articles.

The Working Group aims to develop guidelines for evidence-based nursing, as defined by Behrens (2004): "Integration of the latest, highest level scientific research into the daily nursing practice, with regard to theoretical knowledge, nursing experience, the ideas of the patient and available resources." The Working Group based the text on evidence whenever possible, but if evidence were missing, it was based on best practice.

Four components that influence nursing decisions can be distinguished: personal clinical experience of the nurse; existing resources; patient wishes and ideas; and results of nursing science. This statement implies that, although literature is important, the experience of nurses and patients is also necessary for decision making. Consequently, it is not only the written guidelines that are relevant for nursing practice.

The Working Group included some topics that are not only applicable to intravesical instillation, but decided to include them because they make the guidelines more complete.

Rating Scheme for the Strength of the Recommendations

Grade of Recommendation (GR)

Grade	Type of Evidence - Nature of Recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A blinded review was carried out by specialist nurses, urologists in various European countries and the USA, a patient representative and a representative of a local occupational health and safety organisation. The Working Group revised the document based on the comments received and included relevant references received (also from after the search period). A final version was approved by the European Association of Urology Nurses (EAUN) Board and the European Association of Urology (EAU) Executive responsible for EAUN activities.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Biering-Sorensen F, Bagi P, Hoiby N. Urinary tract infections in patients with spinal cord lesions: treatment and prevention. *Drugs*. 2001;61(9):1275-87. [73 references] [PubMed](#)

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Griffin JG, Holzbeierlein J. Side effects of perioperative intravesical treatment and treatment strategies for these side effects. *Urol Clin North Am.* 2013 May;40(2):197-210. [PubMed](#)

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Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Some of the literature was not easy to grade. However, if the Working Group thought that the information would be useful in practice, it was ranked as level of evidence (LE) 4 and grade of recommendation (GR) C. Low-level evidence indicated that no higher level evidence was found in the literature when writing the guidelines, but cannot be regarded as an indication of the importance of the topic or recommendation for daily practice. The literature used in these guidelines included qualitative research, but because there is no systematic ranking for these types of studies, the qualitative studies were all graded LE 4.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate intravesical instillation with mitomycin C (MMC) or bacillus Calmette-Guérin (BCG) in adults with non-muscle invasive bladder cancer (NMIBC)
- Protecting health care professionals from exposure to antineoplastic drugs

Potential Harms

- All antineoplastic agents are potentially hazardous and must be handled with caution. Although the risks of bacillus Calmette-Guérin (BCG) and mitomycin C (MMC) are different (an attenuated vaccine and a cytotoxic agent), both are on The National Institute for Occupational Safety and Health (NIOSH) Alert List as hazardous drugs. They have the potential to cause carcinogenic, developmental or reproductive toxicity or organ injury.
- Both BCG and MMC are potential health risks to all persons exposed to them during handling. There is no permissible exposure level set for these hazardous drugs. Analysis of occupational exposure of health care workers to these drugs has shown that oncology nurses have the highest exposure rate.

Oncology nurses exposed to carcinogenic agents have an increased incidence of leukaemia and other cancers, as well as genetic mutations noted in their urine because of accidental exposure to carcinogenic agents. Employers must assess the risk of handling antineoplastic and biological drugs and take suitable precautions to protect employees by identifying the hazards, and deciding who might be harmed and how. Exposure during handling of BCG and MMC may be through skin or eye contact, skin absorption, inhalation of aerosols and drug particles, ingestion, and needle stick injuries. Refer to Chapter 6 in the original guideline document for further discussion on safety issues during handling these agents and material exposed to these agents, including patient waste.

- Insertion of a catheter outside an operating theatre is a risk factor for developing bacteriuria. Bacteriuria is acquired at a rate of 1% to 3% per catheterisation. Aseptic technique must be used when inserting the catheter before instillation. To minimise the risk of cross-infection health care professionals should be constantly aware of their hand hygiene.
- Refer to Sections 9.2, 9.3, and 14.3 in the original guideline document for specific side effects of BCG and MMC.

Contraindications

Contraindications

Contraindications for Intravesical Instillations

Intravesical chemotherapy is contraindicated in cases of gross haematuria requiring irrigation, and/or any suspicion of extra- or intraperitoneal bladder perforation. Extravasation of chemotherapy may lead to serious adverse events.

Pregnancy is not an absolute contraindication to mitomycin C (MMC) administration according to the summary of product characteristics (SPC), but given the relatively small benefit of the instillations, the decision to give intravesical chemotherapy during pregnancy is on a case-by-case basis. Breastfeeding should be discontinued during MMC treatment.

Intravesical administration of bacillus Calmette-Guérin (BCG) is contraindicated in patients with gross haematuria, after traumatic catheterisation, for 2 weeks after transurethral resection of bladder tumour (TUR-BT), and in patients with a symptomatic urinary tract infection (UTI). Asymptomatic bacteriuria is not a contraindication. Other contraindications include active tuberculosis, hypersensitivity to BCG, previous radiotherapy of the bladder, pregnancy and lactation. There is evidence that BCG therapy may be safe in immunocompromised patients. BCG administration is not recommended during pregnancy, although relevant data are lacking.

Qualifying Statements

Qualifying Statements

- With an emphasis on delivering these guidelines based on a consensus process, the European Association of Urology Nurses (EAUN) Guidelines Working Group intends to support nurses and practitioners who are already assessed as competent in the procedure of intravesical instillations. Although these guidelines aim to be comprehensive, effective practice can only be achieved if the nurse or practitioner has a clear and thorough knowledge of the anatomy under discussion and the necessary understanding of basic nursing principles.
- This publication focuses on intravesical instillations with mitomycin C (MMC) and bacillus Calmette-Guérin (BCG). These guidelines are intended to complement, or provide support to, established clinical practice and should be used within the context of local policies and existing protocols and with recognition of the individual situation of the patient.

- The EAUN Guidelines Working Group for intravesical instillation has prepared these guidelines to help nurses assess evidence-based management and incorporate the recommendations into their clinical practice. These guidelines are not meant to be prescriptive, nor will adherence to them guarantee a successful outcome in all cases. Ultimately, decisions regarding treatment and care must be made on a case-by-case basis by health care professionals after consultation with their patients and colleagues, and using their clinical judgement, evidence-based knowledge, and expertise.

Limitations of the Document

The EAUN acknowledges and accepts the limitations of this document. It should be emphasised that the current guidelines provide information about treatment and care of individual patients according to a standardised approach. The information should be considered as providing recommendations without legal implications. The intended readership is practising urology nurses and nurses working in a related field throughout Europe. Cost-effectiveness considerations are best addressed locally and therefore fall outside the remit of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Chart Documentation/Checklists/Forms

Resources

For information about availability, see the *Availability of Companion Documents and Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Vahr S, De Blok W, Love-Rettinger N, Thoft Jensen B, Turner B, Villa G, Hrbáček J. Intravesical instillation with mitomycin C or bacillus Calmette-Guérin in non-muscle invasive bladder cancer. Arnhem (The Netherlands): European Association of Urology Nurses (EAUN); 2015 Mar. 88 p. [178 references]

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Not applicable: The guideline was not adapted from another source.

Date Released

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European Association of Urology Nurses - Medical Specialty Society

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Guideline Committee

The European Association of Urology Nurses (EAUN) Guidelines Working Group for Intravesical Instillation

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Members of the Working Group have provided disclosure statements of all relationships that might be a potential conflict of interest. This information is stored in the European Association of Urology (EAU) database.

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Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the European Association of Urology Nurses (EAUN) Web site [\[REDACTED\]](http://www.eaun.org).

Availability of Companion Documents

Various resources including procedures for intravesical instillation, a checklist for patient information, EORTC Quality of Life and side effect questionnaires, and examples of competency and training documents are provided in the appendices in the [original guideline document](#) [\[REDACTED\]](http://www.eaun.org).

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 7, 2015. The information was verified by the guideline developer on November 10, 2015.

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